SIMULATED SPACE RADIATION: MURINE SKELETAL RESPONSES DURING RECOVERY AND WITH MECHANICAL STIMULATION

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Simulated space radiation (SSR) at doses similar to those of solar particle events or a round-trip sojourn to Mars (1-2Gy) may cause skeletal tissue degradation and deplete stem/progenitor cell pools throughout the body. We hypothesized that SSR causes late, time-dependent deficits in bone structure and bone cell function reflected by changes in gene expression in response to anabolic stimuli. We investigated time-dependence of responses in gene expression, cell function, and microarchitecture with respect to radiation (IR) and an anabolic stimulus of axial loading (AL).

Male 16-wk C57BL6/J mice (n=120) were exposed to 0Gy (Sham, n=10), ^{56}Fe (2Gy, n=10), or SSR (1Gy ^{1}H/^{56}Fe/^{1}H, n=10) by total body irradiation. Tissues were harvested 2 or 6 mo. later. Further, we subjected subset of Sham (n=15) and SSR (n=15) to rest-inserted AL starting at 1 and 5 months post-IR (-9N, 60 cycles/day, 3 days/wk, 4 wks). Samples were harvested from a subset of Sham-AL (n=5) and SSR-AL (n=5) after a week to measure changes in gene expression levels.

Exposure to ^{56}Fe caused a significant reduction in cancellous bone volume fraction (BV/TV) compared to Sham (-34%) and SSR (-20%) in the tibia metaphysis at 2-months post-IR; however BV/TV for SSR group was not different than Sham. Both ^{56}Fe and SSR caused significant reduction in trabecular number (Tb.N) compared to Sham (-33% and -16%). Tb.N for ^{56}Fe was significantly lower than SSR (-21%). *Ex vivo* culture of marrow cells 6 months post-IR showed that both ^{56}Fe and SSR exposures significantly impaired colony formation (-66% and -54%), as well as nodule mineralization (-90% and -51%) compared to Sham. AL increased BT/TV and Tb.Th and IR reduced BV/TV and Tb.N, at both time points. AL increased expression of the antioxidant response gene *Nfe2l2* and the osteoprogenitor-associated marker *Runx2* in the bone marrow cells and mineralized tissue. Significant effect of radiation in *Runx2* expression at both time points indicated a persistent effect of radiation in the marrow cells. AL, but not IR, significantly increased expression of *periostin*, as well as *Gadd45a*, which is upregulated by ionizing radiation. Changes in gene expression levels were diminished at the later time point.

SSR had lasting effects to inhibit osteogenic differentiation on bone marrow, stem and osteoprogenitor cells. Irradiation caused persistent changes in expression of select genes in cells from the marrow but not mineralized tissue compartment of bone. Contrary to our hypothesis, SSR did not impair the ability of cancellous bone to respond to AL. Hence, mechanical stimulus may be a potential countermeasure against IR-induced bone loss.

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